Response to Wyden, Grassley Request for Comment on Sovaldi Report

1. What are the effects of a breakthrough, single source innovator drug on the marketplace?

The desired effect of a breakthrough, single source innovator drug is that it fills existing gaps in treatment of a medical condition i.e. it addresses an unmet healthcare need. However, from this point on, the broader impacts of such breakthroughs in healthcare diverge from those of similar breakthroughs in non–healthcare markets. In these markets, the innovative product gets copied by competitors and the resulting competition leads to lower costs and broad adoption, which yields higher value for consumers in the marketplace. In healthcare, and especially in the health technology space, this dynamic plays out differently.

Pharmaceutical manufacturers operate against a backdrop of fundamental economic uncertainty because only a small number of the products that they invest in actually make it to market, and so the returns generated from those products must be high enough to cover the costs of the others that failed to make it to market. As a result, a single source breakthrough innovator drug spurs "copycat" development as pharmaceutical manufacturers move to invest where there is a high probability of guaranteed returns. If one manufacturer brings a blockbuster to market, then others will try and bring similar products. However, unlike non–healthcare markets where more normal supply and demand dynamics govern market transactions, in healthcare, due to regulations that grant pricing power (patent protection), access to substantial customer segments (via rules that FDA approved drugs be available to certain healthcare programs) and the development economics of the pharmaceutical industry, these competing products are shadow priced to generate returns similar to those of the breakthrough innovator drug. So in contrast with non–healthcare markets, where competition spurred by innovation leads to lower costs for consumers, in health technology, competition, in the initial patent exclusivity phase, simply serves to sustain high costs. To put it more simply, a salient effect of a breakthrough, single source innovator drug on the marketplace is that it spurs "me too" innovation[1] with follow on drugs at non-competitive prices leading to increasing costs.

Since the incentive to maximize returns from a successful drug is strong, a number of second order effects also occur later on downstream from the product's launch. These effects are common to most products in the pharmaceutical sector (not just to single source breakthrough innovator drugs) and can take a variety of forms:

- Extending the drug's life cycle through off–patent use, where the drug is used treat conditions that it was not originally developed for. There is little incentive to evaluate an existing drug for additional uses to the extent required for FDA approval. However, drug companies encourage off-label prescribing with even cheaper studies than the FDA requires, but this off-label use lacks strong evidence of safety and effectiveness, which in turn increases the potential for unsavory outcomes. According to a recent study,

[1] "The Effect of Price Controls on Pharmaceutical Research", David Francis, National Bureau of Economic Research Digest, May 2005.

off-label use is associated with a 44 percent greater risk of having an adverse event or side effect than with on-label use.[2]

- Patent "evergreening" in which manufacturers secure a new patent for the drug by making minor modifications to it such as changing the dosage, or the drug's packaging, or making minor modifications to its chemical composition, thereby maintaining the patent protection and associated price.
- Implementation of measures such as pay–to–delay deals with generic rivals where a brand-name drug maker settles a patent lawsuit by paying cash or transferring something else of value to delay launching a copycat medicine once the new drug goes off–patent.

Ideally, a breakthrough single source innovator drug should foster competition amongst other players in the marketplace. Competitors should be spurred to develop their own solutions for other conditions that could provide them with the benefits that normally accrue to single source breakthrough products. Unfortunately though, in practice, it seems breakthrough single source innovator drugs lead initially to closing of treatment gaps followed by "me-too" innovation, and later to suboptimal allocation of resources for the primary purpose of protecting the product's existing income streams.

2. Do the payers in the programs have adequate information to know the cost, patient volume, and increases in efficacy of a new treatment regimen?

The short answer is that information available to payers today about new treatments is not conducive to estimating costs reliably, and only enables relatively low value estimates for patient volumes and treatment efficacy.

Cost, or unit price, is the single most difficult factor to predict for a new treatment regimen today. Traditionally, payers used historical information to develop cost estimates for new treatments. These estimates were not meant to be precise projections, but rather an attempt to project expected costs into the "right ball park". However, in the last few years, new treatment pricing has deviated to such an extent from historical norms that it is very difficult to know the cost of a new treatment ahead of its release. Whether it's the new cancer drugs, or Sovaldi, or cholesterol lowering PCSK9 inhibitors, or new cystic fibrosis treatments, wholesale acquisition price (WAC) as established by manufacturers has far exceeded expectations to the extent where it is very hard to believe that it is being driven by actual development costs. Given that manufacturers are pricing new treatments to maximize revenue and not access, and patent laws grant them monopoly pricing power, the traditional data and methods used by payers to estimate costs are no longer equal to this task.

Estimating patient volume for new treatment regimens is also at best an inexact science. For some conditions (e.g. rare types of cancer or hereditary diseases), it is relatively simple to estimate patient volume. However, for other conditions, the best analysis only yields wide ranges of potential patient volume. For instance, the new cholesterol lowering drugs known as PCSK9 inhibitors that were recently released on the market have a number of patient segments that they could be deployed for. They could be used for people with high cholesterol,

[2] "Association of Off-label Drug Use and Adverse Drug Events in Adult Population", Eguale, MD PhD, Buckeridge, MD PhD, et al, JAMA Internal Medicine, January 2016

people with high cholesterol who are resistant to current medications, people with a history of coronary artery disease, or even as preventive therapy for people with family histories of high cholesterol or heart disease. Depending on which combinations of these potential patient segments end up getting the treatment, the resulting patient volume could end up varying significantly from the original utilization projections. Similarly, payers may be able to assess patient volume for a cancer treatment based on its intended usage, but have no way to assess how the patient volume would vary if the treatment starts being applied for cancers that weren't targeted during its development. Finally, in government programs such as Medicare, Medicaid, and Marketplace, patient volume estimates are further impacted by the uncertainty regarding how program specific regulations will be applied to benefit management tools (such as placement on preferred drug lists (PDLs), prior authorization review) for these treatments. The proper use of these tools can affect overall patient volumes and total costs for these treatments, and not knowing what limits program administrators may place around them dilutes the viability of patient volume projections that payers develop.

Assumptions about the efficacy of a new treatment regimen are based off of clinical trials because those trials provide detailed and validated data. In practice, however, the real-world effectiveness of the product is often lower. Patients in clinical trials are carefully selected; they receive treatment at leading institutions; and their adherence to the care plan is tightly monitored. Under real-world conditions, patients might have more comorbidities that interfere with treatment or be subject to lifestyle factors that result in lower adherence. This sort of underperformance in the real world relative to clinical trials performance is exacerbated by the newly noticed tendency of manufacturers to withhold critical information about adverse side effects that have been observed in the clinical trials.[3] Additionally, clinical trials data does not provide guidance on harmful side effects that may develop over time with extended exposure to the treatment and which may detract from its overall efficacy.[4] As a result, payers generally treat efficacy estimates that accompany the release of a new treatment regimen with cautious skepticism.

3. What role does the concept of ''value'' play in this debate, and how should an innovative therapy's value be represented in its price?

In general, creating and delivering value is how businesses generate and sustain competitive advantage. In the healthcare market, value associated with treatments should be considered along five main dimensions:

a. The degree to which a treatment alleviates the burden of a medical condition (does it cure it? does it mitigate the pain and adversity associated with it? does it restore quality of life for those afflicted with it?)
b. The length of time over which the impact of a treatment can be sustained.
c. The size of the population segment that may benefit from the treatment vs. the total size of the population that may be treated with the drug.
d. The timeline under which the benefit(s) may be seen.

[3] "Completeness of Serious Adverse Drug Event Reports Received by the US Food and Drug Administration in 2014", Moore, Furberg et al, Pharmacoepidemiology and Drug Safety, February 2016
[4] "Pfizer Facing Growing Number of Lawsuits over Lipitor's Side Effects", Laura Lorenzetti, Fortune, August 8, 2014

e. The cost associated with the treatment.

Using this framework, high value would be associated with treatments that deliver the most durable alleviation of disease burden near-term for the largest number of affected people *at the lowest relative cost*. This last part is perhaps the most important. Healthcare like all other sectors of the economy has finite resources and high cost treatments force tradeoffs that can offset any gains they deliver. These tradeoffs can present through two main channels:

- For public healthcare programs, these tradeoffs may come in the form of reduction in other healthcare services and treatments, or at a macro-level, reductions in other non-healthcare, but equally vital public programs like education and infrastructure development. For consumers in the private market, they may come in the form of much higher prices that force reductions in other discretionary spending or the forgoing of healthcare spending altogether.
- High cost treatments can also reduce the number of people in their target population segment that can access the treatment which leads to a much smaller impact on system wide health outcomes.

The high cost of Gilead's Hepatitis C drug, Sovaldi, is a good case study of the effects outlined above. In California, the California Technical Assessment Forum, an expert panel drawn from hospitals, insurers and patient advocacy groups, recommended that the treatment be restricted to only the sickest of those afflicted with Hepatitis C as the cost of making it widely available would put an unbearable financial strain on the state's finances. As a result of similar decisions in other states, driven largely by the drug's exorbitant price, only a small fraction of the 3,500,000 Hepatitis C sufferers in the US have received this treatment so far. The key point here is that the high cost is restricting access, and straining healthcare budgets which in turn reduces the relative value of the treatment. Conversely, if the drug had been priced significantly lower, it would have been a higher value product since many more people could have been treated with it. The overall performance gains for the nation's healthcare system would have been greater, and Gilead could still have generated substantial returns on its investment based on higher utilization volumes.

Another combination that reduces value is when a treatment combines high costs with minimal improvements in alleviating disease burdens. Unfortunately, this sort of low value dynamic is emblematic of a substantial amount of high cost treatments offered in the US today. For instance, a recent evaluation found that while over the past decade the price of a cancer drug has risen from $4,500 a month to over $10,000 a month, there is no correlation between these prices and the drugs' actual performance as measured by a range of industry standard metrics like cost-efficacy (CE) ratios, prolongation of patient life in years, or quality-adjusted life-years (QALYs).[5] In fact, more and more, research suggests that cancer drugs while increasing in price are delivering diminishing returns in terms of healthcare outcomes with a recent study estimating that in 2013, one extra year of life for cancer patients cost $207,000, on average, nearly quadruple what it did in 1995.[6] Similarly, the new cystic fibrosis drug released by Vertex last year arrived with a very high price tag ($300,000+ per year), but by the manufacturer's own admission provided negligible additional efficacy over older treatments.

[5] "Cancer Drugs in the United States: Justum Pretium—The Just Price", Kantarjian, Fojo, et al, Journal of Clinical Oncology, May 6, 2013.
[6] "Pricing in the Market for Anticancer Drugs", Howard, Back, et al, Journal of Economic Perspectives, Winter 2015

In summary, the highest value is created by treatments providing clinical efficacy improvements relative to older treatments (i.e. more sustainable alleviations in disease burden) at a price point that enables wide access which in turn lead to improved outcomes on a scale where they can have a tangible impact on quality and/or costs for the entire healthcare system. It should be evident by now that price is the single biggest determinant of value. A new treatment with low efficacy gains compared to prior treatments marketed at an affordable price (i.e. a price that enables wide access for the target population) is higher value compared to a treatment that delivers higher efficacy gains but comes at an unaffordable price that restricts access and strains financial resources to a point where enabling wide access to these treatments necessitates benefit reductions elsewhere.

4. What measures might improve price transparency for new higher-cost therapies while maintaining incentives for manufacturers to invest in new drug development?

There is no connection between price transparency for new higher-cost therapies and incentives for manufacturers to invest in drug development. It is almost a non-sequiter to consider that lack of price transparency somehow incentivizes investment. The only way this would be true is if lack of price transparency somehow directly supports the economy leading profit margins that this industry sector generates, [7] which in turn would imply that those margins are driven by exorbitant pricing and are not truly reflective of actual costs. If prices reflected the true costs of drug development and marketing, then price transparency would only serve to validate the value proposition for pharmaceutical manufacturers, rather than being a disincentive for investment.

Price transparency would provide purchasers with visibility into pharmaceutical manufacturers' investment and production costs and the degree to which prices for new drugs were covering those costs and driving returns. Such an understanding of business fundamentals would support value-based assessments of these drugs. Moreover, price transparency for pharmaceutical manufacturers would be neither a radical nor novel measure. All other major participants in the healthcare sector are subject to such measures in some form. CMS accounts for the average cost of medical procedures when it sets prices for providers and hospitals for the Medicare program. Health insurance companies have to file detailed information with regulators on claims costs, unit costs, administrative costs, trend projections, etc. when they submit rates, which themselves are subject to regulatory approval, and their subsequent performance is subject to financial limits like medical cost ratio (MCR) floors. Price transparency measures for the pharmaceutical sector would simply be extending norms already in place for much of the rest of the healthcare industry to it.

Acknowledging the risks involved in developing treatments, and how those risks can skew investment towards a select group of therapies where the chances of generating high returns are more stable, one measure that could incentivize investment in new drug development would be for the government to increase spending on basic and applied research in the health technology space. This would yield more of the foundational breakthroughs (for e.g. genome sequencing, etc.) that drug developers could then leverage and build on to develop new treatments. Basically, greater investment in "the Commons" for the pharmaceutical industry could lower the

[7] "The Most Profitable Industries in 2015", Liyan Chen, Forbes, September 23, 2015.

relative research and development expenses associated with new treatments by providing more prospective treatments with good probability of success thereby generating greater activity in this area.

5. What tools exist, or should exist, to address the impact of high cost drugs and corresponding access restrictions, particularly on low-income populations and state Medicaid programs?

For state Medicaid programs, and the low-income populations they serve, a number of tools exist today that if deployed effectively and in a disciplined manner would have a material impact on the high cost of drugs. In no particular order of importance, these are:

- **Preferred drug lists (PDLs)** – in normal markets, consumers have access to transparent prices enabling price comparisons for desired goods and services, and are in a position to make rational decisions on how much they pay for their preferred goods and services. This informed choice drives demand and supply in the market. Unfortunately, in healthcare, ordinary consumers are not in a similar position. The complexity of healthcare means they largely cede decision making to their healthcare providers without much visibility into the costs. However, entities that act as purchasers of healthcare goods and services – federal and state governments and health insurance providers – should partner together to perform this function. In order to do this effectively, they should be enabled to leverage the power of choice through an easy to use regulatory mechanism. Put simply, they should be able to exclude any drug from their preferred drug lists (PDLs) and formularies whose cost exceeds its proven clinical value for the population at risk. This may extend to an entire drug class and not just an individual drug. Government programs serve a substantial portion of the medically vulnerable people in the country, and access to them is an important business prerogative for pharmaceutical companies. Effective use of PDLs would be a sound way to signal that treatment prices must correlate with value for the products to have access to the people served by these programs.
- **Utilization management approaches** – health insurance providers, especially those serving the Medicaid population, should be empowered to use utilization management tools such as prior authorization review, step therapies, etc. to ensure that high cost drugs are used strictly to treat the conditions that they were specifically developed for and in accordance with the most current evidence-based clinical standards, targeting the patient populations most likely to get benefit from taking the drug(s). This would enable them to maximize the value derived from these treatments while limiting the potential harm that can be caused by over utilization or prescription drug abuse.

Another tool that can help to control the costs of high priced prescription drugs and which can be deployed throughout the healthcare system (and not specifically in Medicaid) is:

- **Product design features to influence spending** – health insurance providers use cost sharing (co-pays, deductibles, coinsurance) to signal the cost effectiveness of various drug treatments, so that consumers can make financially informed decisions about the drugs they purchase and they should be allowed to utilize these product design features for maximum impact. A number of proposals for

addressing prescription drug costs have focused on capping consumer co-pays as one way to address this issue. This is a misguided approach that will have no impact on overall prescription drug costs. The reason is that health insurance premiums and cost sharing designs are inversely related. Capping or reducing co-pays will only lead to the overall cost being shifted into higher premiums for the consumers. This is a feature and not a bug of insurance product design – lower cost sharing means that the health insurance provider is picking up more of the overall costs, which in turn leads to higher premiums. This is why platinum plans (which have very low cost sharing levels) sold on the marketplaces set up under the ACA are also the highest priced plans while bronze plans (which have higher cost sharing levels) are the cheapest plans.

Finally, some other measures, which currently are not in place today, but which could help control costs and ensure appropriate access to treatments for consumers are:

- **Enrollment lock-in periods for members in certain government programs** – people being served by health insurance providers in government programs designed for those who are high risk, and chronically sick should be subject to an enrollment period "lock-in" of at least twelve months. These folks tend to switch health insurance providers so they can shop for doctors who will prescribe the medications they want rather than the ones they need. Such behavior dilutes the impact of the care management programs that the health insurance providers are using to improve the members' health conditions and exacerbates prescription drug abuse in this population – a risk that is particularly high given that these folks often suffer from multiple chronic ailments. Moreover, enrollment lock-in periods will also enable payers investing in expensive treatment regimens to deliver the treatment over a timeframe that is adequate for realizing the promised benefits from it.
- **Restrictions on pharmaceutical advertising and marketing to consumers** – such measures would ensure that prescriptions would be driven by clinicians and based on professional assessments of people's healthcare conditions and needs rather than by customer demand influenced and skewed by marketing and advertisements.
- **Varying patent protection periods based on price** – a patent system that varied the exclusivity period by value could spur a rethink in how manufacturers set prices. More specifically a patent system that awarded high value treatments (drugs that provide efficacy gains at reasonable price points that enable wide access to the treatment) would get longer exclusivity periods, while low value treatments would get shorter exclusivity periods. Such a system would change pharmaceutical manufacturers' internal calculus on the kind of pricing that would maximize returns for their products.